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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/635,171	08/06/2003	Dieter Heindl	21339-US	1366

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/635,171	HEINDL ET AL.	
	Examiner	Art Unit	
	Amanda M. Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-10,14,15 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10,14,15 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on January 16, 2007 has been entered.

Claims 1, 4-10, 14-15, and 27 are currently pending. Claim 1 has been amended. The Applicant's arguments have been fully considered. All rejections not reiterated herein are hereby withdrawn. This action is non-final.

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-10, 14-15 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-10, 14-15 and 27 are indefinite over the recitation of the phrase "substantially complementary". This phrase in considered indefinite because it is not clearly defined in the specification and there is no art recognized definition for this

phrase.

Claims 1, 4-10, 14-15 and 27 are indefinite over the recitation of the phrase "said fluorescent entity being either a FRET donor entity or a FRET acceptor entity". This phrase in considered indefinite because the claims as written encompass pairs of probes wherein both members of the probes have FRET donor entities, both members of the pairs have FRET acceptor entities, and wherein one member of the pair has a FRET donor entity and the other member has a FRET acceptor entity.

Claims 1, 4-10, 14-15 and 27 are indefinite over the recitation of the phrase "wherein the spacer entities of the FRET hybridization probes are capable of forming non covalent interactions with each other". Capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear as to whether the probes do in fact form non-covalent interactions with each other or only have this ability under some under some unspecified conditions or following some unstated modification of the oligonucleotides. This phrase is also indefinite because it is unclear if the pair of FRET probes hybridize to each other only in the presence of the target or if the pair can hybridize when the target is absent due to the non-covalent interactions between the spacer regions.

Claim 1 recites the limitation "the sequence of the target nucleic acid". There is insufficient antecedent basis for this limitation in the claim because although the claim previously refers to a “target nucleic acid sequence” it does not refer to “a sequence of the target nucleic acid”.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 5, 10, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (US Patent 6130047 Issued 10/2000) in view of Kurata (Nucleic Acids Research 6/2001).

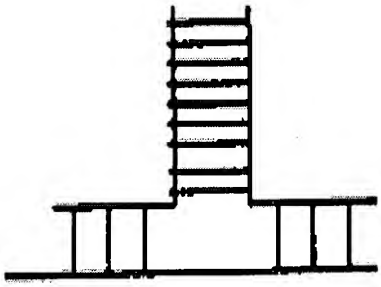
Regarding Claim 1, Nadeau et al teach a composition comprising a pair of FRET hybridization probes capable of hybridizing to a target nucleic acid sequence. Each probe comprises a nucleotide sequence entity that is complementary to a region of the target, a fluorescent entity (FRET donor or acceptor), and a spacer entity that connects

the nucleotide sequence entity and the fluorescent entity; wherein the FRET hybridization probes hybridize adjacently to each other on the target nucleic acid; and wherein the spacer entities of the FRET hybridization probes are capable of forming non covalent interactions with each other. Specifically Nadeau et al teach a detector nucleic acid comprising a 3-way oligonucleotide junction structure and two donor/acceptor dye pairs. The detector nucleic acid comprises: a target oligonucleotide (labeled at the 5' end with fluorescein), a first oligonucleotide (labeled at the 3' end with fluorescein), and a second oligonucleotide (labeled at the 5' and 3' ends with dabcyl) (Example 3). The following illustrates the teachings of Nadeau: the nucleotides in underlined are the spacer entities. As you can see they hybridize to each other. The first oligo is attached to a fluorescein and the second is attached to dabcyl. The italicized part of the first oligonucleotide hybridizes the italicized part of the target sequence and the bolded part of the second oligonucleotide hybridizes adjacent to the first oligonucleotide on the bolded part of the target sequence. This would look like the figure below.

Target SEQ 5'flourescein-**GGAGCGAGCG***AAGTGTCCTGGC*TAGAGTCTTCAAATATCAGAGCTTTACCTAACAA 3'

First Oligonucleotide 5'*GCCAGGACAC*GGAGAGG-flourescein-3'

Second Oligonucleotide 5' dabcyl-CCTCTCC**CGCTCGCTCC**-dabcyl 3'



Nadeau et al do not exemplify a method wherein the spacer entities of the FRET hybridization probes are capable of forming non-covalent interactions with each other, wherein the noncovalent interactions consist of A/T base pair interactions.

However Nadeau et al does teach that the probe sequences are selected such that there is stable hybridization between the probes when the junction structure is hybridized to the target and the probes are destabilized and at least partially dissociated when the junction structure is not hybridized to the target. Nadeau et al further teach that the Tm of the probes may be used as is known in the art to adjust the sequences of the probes to obtain this result, and it is generally selected to be approximately equal to or less than the reaction temperature. The length and nucleotide composition of the sequences involved in base pairing is one factor affecting the Tm, with shorter sequences and relatively AT rich sequences generally contributing to a lower Tm (Column 8).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the probes of Nadeau et al by designing probes wherein the spacer regions consist of A/T base pairs in situations when it is

desirable to perform a hybridization reaction at a low temperature. It was well known in the art at the time of the invention that A/T base pairs have a lower melting temperature than C/G base pairs. Thus it would have been obvious to an ordinary artisan to design probes that are approximately equal to or less than the reaction temperature by modifying the A/T content of the probes.

Additionally Kurata et al teach that they studied the quenching effects that guanine bases can have BODIPY FL fluorescence. To identify the composition of bases that causes BODIPY FL fluorescence to be quenched, they designed 4 model probes with BODIPY FL at the 5' end and measured the fluorescence intensities of the probe solutions before and after adding a target DNA. Of the four sets of probes and targets, a significant decrease in fluorescence intensity was observed only when the probe C9T6 was hybridized with the target A6G12. Moreover, probe G9A6 was much less fluorescent than the others even before hybridization. Both of these finding suggest that a G position in very close proximity to BODIPY FL can quench fluorescence (Page 2). Kurata et al also designed various probes with G's placed at different positions throughout to estimate their effect on the BODIPY FL fluorescence and found that significant quenching cause by intermolecular interaction between G and BODIPY FL occurred only when the G was at the 5' end of the probe (Page 3).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the probes of Nadeau et al by designing probes wherein the spacer entities consist of A/T base pairs. It was well known in the art at the time of the invention that guanine bases at the 5' end of an oligonucleotide

probe could quench the fluorescence of a fluorescent dye conjugated to the probe. Therefore it would have been obvious to an ordinary artisan to design probes wherein the spacer entities consisted of only A/T base pairs in situations where a fluorescent dye is being used to minimize the quenching effect of guanine residues.

Regarding Claim 27, Nadeau et al teach a reaction mixture for use in a dependent nucleic acid amplification reaction, comprising, in a solution: a pair of hybridization probes and at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction. Specifically Nadeau et al teach they prepared a solution containing, 50 mM TRIS-HCl, pH 8.0, 10 mM $MgCl_2$, 50 mM NaCl, 10 mM dTTP, 10 mM dCTP, 10 mM dGTP, 10 mM dATP, 5 units exo- Klenow, and varying amounts of the 3-way junction detector nucleic acid were prepared and placed in an SLM 8100 fluorometer with the sample chamber preheated to 37°C (Example 3).

5. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047 Issued 10/2000) in view of Kurata (Nucleic Acids Research 6/2001) as applied to claims 1, 5, 10, and 27 above and in further view of Wittwer (U.S. Patent 6140054 Issued 10/2000).

The teachings of Nadeau and Kurata are presented above.

The combined references do not teach a set of FRET probes wherein the fluorescent entities of the probes are selected from the group consisting of fluorescein/Cy5, fluorescein/LC Red 640, fluorescein/LC Red 705, and fluorescein/JA286.

However, Wittwer et al teach that acceptable fluorophore pairs for use as fluorescent resonance energy transfer pairs are well know to those skilled in the art and include, but are not limited to, fluorescein/rhodamine, phycoerythrin/Cy7, fluorescein/Cy5, or fluorescein/Cy5.5.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau and Kurata by using one of the fluorophore pairs suggested by Wittwer because they are an equally effective means for detecting nucleotides via FRET technology.

6. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047 Issued 10/200) in view of Kurata (Nucleic Acids Research 6/2001) as applied to claims 1, 5, 10, and 27 above, and in further view of Fisher (U.S. Patent 6054568 Issued 4/2000).

The teachings of Nadeau and Kurata are presented above.

The combined references do not teach a composition wherein at least one of the hybridization probes includes a nucleotide having a non-natural base selected from the group consisting of a 7-deazapurine, a diamino purine and a C-nucleotide.

However Fisher et al teach during primer and probe experiments higher affinity and/or specificity to complementary nucleic acids may be achieved by the using nucleobase analogs (i.e. isoguanine and 7-deaza-isoguanine) (Column 8, lines 4-22).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau and Kurata so as to have used a probe containing at least one non naturally occurring base in order to have achieved the benefits set forth by Fisher which include improving the affinity and specificity of the probe hybridizing to the complementary nucleic acids.

7. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047 Issued) in view of Kurata (Nucleic Acids Research 6/2001) as applied to claims 1, 5, 10, and 27 above, and in further view of Acton et al (U.S. Patent 6228581 Issued 5/2001).

The teachings of Nadeau and Kurata are presented above.

The combined references do not teach wherein at least one of the hybridization probes includes a modified sugar-phosphate backbone that contains either a 2-O methyl group or a phosphothioate.

However, Acton et al teach that nucleic acids which can be used as probes or primers can be modified to become more stable. Examples of such nucleic acids are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (Column 24, lines 65-68).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau and Kurata so as to have used a probe containing a modified sugar phosphate backbone in order to have achieved the benefits set forth by Fisher which include having a more stable nucleic acid.

8. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047 Issued 10/2000) in view of Kurata (Nucleic Acids Research 6/2001) as applied to claims 1, 5, 10, and 27 above, and in further view of Urdea et al (U.S. Patent 5635352 Issued 6/1997).

The teachings of Nadeau and Kurata are presented above.

The combined references do not teach a composition wherein said spacer entity is branched:

However, Urdea et al teach a composition wherein a spacer entity is branched. Specifically Urdea et al teach amplification multimers, which are constructed so as to contain a first segment that hybridizes specifically to the nucleic acid, and a multiplicity of second segments that hybridize specifically to a labeled probe. The multimers may be either linear or branched. Branched multimers may be in the shape of a fork or a comb, with comb-type multimers preferred (Column 2, lines 1-14).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Nadeau and Kurata so as

to have used branched linkers in order to provide signal amplification in hybridization assays through networks of labeled probes. Branched mulitmers provide a convenient way to covalently attach more than one dye to an oligonucleotide.

9. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nadeau et al (U.S. Patent 6130047 Issued 10/2000) in view of Kurata (Nucleic Acids Research 6/2001) as applied to claims 1, 5, 10, and 27 above, and in further view of Ahern (The Scientist).

The teachings of Nadeau and Kurata are presented above.

The combined references do not teach the packaging of FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates and a buffer suitable for use in a template dependent nucleic acid amplification reaction into a kit.

However, reagent kits for performing nucleotide detection assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have

packaged the FRET probes along with at least one other component selected from the group consisting of nucleic acid amplification primers, a template dependent nucleic acid polymerase, deoxynucleoside triphosphates or a buffer in a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect nucleotide sequences using FRET probes.

Conclusion

10. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

DIANA JOHANNSEN
PRIMARY EXAMINER